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The Examiner's concerns have been rendered moot by the amendments submitted herewith. Specifically, with respect to claim 4, the specification has been amended to recite the limitation on the melting temperature and claim 12 has been amended to further limit claim 10.

In view of the above amendments and remarks, reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 112, is respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 103

Claims 1-5 stand rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Weighardt et al., *PCR Meth.Appl.* 3:77-80 (1993). This rejection is respectfully traversed.

Applicants' invention, as defined by amended claim 1, distinguishes over the art by providing single-stranded oligonucleotide DNA primers having a common 5' universal primer sequence with no homology to any target sequence and a unique 3' target specific sequence that can be pooled together and used in a single PCR reaction to simultaneously amplify multiple target sequences in a sample using only one set of cycling times and temperatures despite differences in respective annealing temperatures among the unique target sequence specific domains and complements thereof.

Weighardt et al. neither teach nor suggest oligonucleotide primers that can be pooled together and used under a single set of cycling times and temperatures to simultaneously amplify multiple target sequences in a multiplex polymerase chain reaction regardless of any differences in the respective annealing

temperatures among the target sequence specific domains of the primers.

To the contrary, Weighardt et al. disclose two multiplex scenarios neither of which teaches or suggests the present invention. In the first scenario, Weighardt et al. disclose a two-step amplification wherein a series of extensions are performed under cycling conditions optimal for the first primer having a lower annealing temperature, and thereafter, adding the second primer having a higher annealing temperature followed by a series of extensions performed under cycling conditions optimal therefor. Unlike Applicant's invention, the aforementioned method does not accomplish simultaneous amplification of multiple target sequences present in a sample under a single set of reaction conditions.

Similarly, the second scenario of Weighardt et al. does not teach or suggest Applicant's invention. Specifically, this scenario discloses two primers each having different annealing temperatures, pooled together in a single reaction mixture but having distinct cycling conditions to optimize conditions for the individual annealing requirements of the respective primers. The second scenario, therefore, does not teach or suggest simultaneous amplification of multiple target sequences in a single reaction under a single uniform set of cycling times and temperatures. Accordingly, Applicant's invention is patentable over Weighardt et al.

Claims 6-12 stand rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Picci et al., *Hum. Genet.* 88:552-556 (1992) in view of Weighardt et al. This rejection is respectfully traversed.

Applicant's invention as defined by claims 6-12, distinguishes over the art by providing methods and compositions for simultaneously amplifying multiple target sequences (present in one or more samples) with a plurality of chimeric primers, under a single set of "universal" PCR cycling conditions (e.g., times and temperatures) in which melting, reannealing and synthesis of each target sequence occurs under identical times and temperatures.

Picci et al. does not teach or suggest invention methods. Instead, Picci et al. teaches away from invention methods by disclosing the necessity for sequential addition of individual primer pairs into a reaction to amplify multiple target sequences. Picci et al. teach away from invention methods which dispense with the requirement for additional time-consuming manipulations of optimizing cycling conditions for primers having distinct annealing requirements.

Further reliance upon Weighardt et al. does not cure the deficiencies of Picci et al. Applicant respectfully disagrees with the Examiner's assertion (page 6, lines 1-9 of Paper No. 6) that one of ordinary skill in the art at the time of the present invention

would have been motivated to modify the primers in the method of Picci et al. to contain a 5' sequence providing a high stringency binding site . . .

Weighardt et al. neither teach nor disclose any sequence that provides a high stringency binding site. Nor does Weighardt et al. teach or suggest compositions or characteristics that provide such site(s). Furthermore, as evidenced by the two alternative methods disclosed, the tailed primers of Weighardt et al. cannot be used together using a single set of cycling conditions to

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simultaneously amplify multiple target sequences present in a sample.

Invention methods and compositions distinguish over the prior art by imposing a uniformly high degree of specificity on the annealing reactions that occur between different primers present in the reaction mixture and their cognate target sequences in the DNA template which results in normalizing the annealing efficiency of different primers as well as the degree of amplification of distinct target sequences. Neither reference, taken alone or in combination teach or suggest Applicant's invention.

It is respectfully submitted that the combined references are incapable of motivating one of ordinary skill in the art to practice invention methods. Accordingly, Applicant's invention is patentable over Picci et al. in view of Weighardt et al.

In view of the above amendments and remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103 is respectfully requested.

SUMMARY

Applicant appreciates the Examiner's thorough consideration of the subject application, as amended. In view of the above amendments and remarks, reconsideration and favorable action on all pending claims is respectfully requested. If any questions or issues remain, the Examiner is invited to contact the undersigned at the telephone number set forth below so that a prompt

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disposition of this application can be achieved. All correspondence should be directed to the address noted below.

Respectfully submitted,

02/10/97

Date

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